Spironolactone is not Effective for the Treatment of Hypokalemia in Peritoneal Dialysis Patients

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Background: Hypokalemia is a common problem in patients on continuous ambulatory peritoneal dialysis (CAPD). We evaluated the efficacy and safety of spironolactone in CAPD patients with hypokalemia.
Methods: We reviewed the clinical response of 12 consecutive hypokalemic CAPD patients treated with spironolactone in our dialysis center.
Results: All patients received spironolactone 25 mg daily. There was no significant change in the serum potassium level after administration of spironolactone (3.30 ± 0.26 *vs.* 3.46 ± 0.38 mmol/L, $p = 0.28$), even though three patients required regular oral potassium supplementation. There was also no significant change in arterial blood pressure or urine output after spironolactone treatment. Spironolactone was well tolerated and no hyperkalemia was recorded.
Conclusion: Spironolactone is not effective in the treatment of hypokalemia in stable CAPD patients, but the agent is well tolerated, at least in CAPD patients with little residual renal function. Future studies are warranted to determine the therapeutic role of spironolactone in CAPD patients with concomitant congestive heart failure or cardiovascular disease. [*Hong Kong J Nephrol* 2007;9(1):36–40]

Key words: hypokalemia, renin–angiotensin system, renal failure, spironolactone

背景：對於接受連續性攜帶式腹膜透析 (CAPD) 的病人，低鉀血症是常見的問題。本研究在出現低鉀血症的 CAPD 病人間，調查了 spironolactone 的功效及安全性。
方法：以本透析中心連續 12 位的低血鉀 CAPD 病人為對象，調查人員回顧了 spironolactone 所產生的臨床反應。
結果：所有病人每天均接受 spironolactone 25 mg，其血清鉀濃度並未在 spironolactone 療程後出現改變 (3.30 ± 0.26 *vs.* 3.46 ± 0.38 mmol/L，$p = 0.28$)，即使期間曾有 3 位病人需要定期口服鉀補充劑。同時，spironolactone 亦未導致動脈性血壓或尿量的明顯改變。治療期間，spironolactone 的耐受性良好，亦未出現高鉀血症的現象。
結論：在病情穩定的 CAPD 病人間，spironolactone 對低鉀血症並不具明顯療效，但耐受性良好，至少對於殘餘腎功能低下的 CAPD 病人而言。至於 spironolactone 對同時患有鬱血性心衰竭或心血管疾病的 CAPD 病人，是否具有任何療效，則仍有待進一步的查證。

Introduction

Hypokalemia is a common complication among patients undergoing continuous ambulatory peritoneal dialysis (CAPD). It is found in 10–36% of CAPD patients [1–3], and may be associated with increased cardiac morbidity and mortality in such patients [4]. The recommended serum potassium concentration is 3.0 mmol/L and above in asymptomatic patients, and greater than 3.5 mmol/L in patients taking digoxin or with a history of cardiac arrhythmias [5].

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Hypokalemia can be corrected by oral supplementation and/or intraperitoneal potassium administration. The compliance of potassium supplementation, however, is often poor. Although potassium loss in the dialysate and poor oral intake are the major causes of hypokalemia in most patients, gastrointestinal loss is often considerable [6–10]. In fact, potassium conductance is present in colonic epithelium [11], and colonic potassium excretion is under the influence of renin-angiotensin-aldosterone axis [12,13]. In this study, we evaluated the efficacy and safety of spironolactone, an aldosterone antagonist, in CAPD patients with hypokalemia.

Patients and Methods

We reviewed 12 consecutive hypokalemic CAPD patients treated with spironolactone from January 2003 to September 2004 in our dialysis center. Serum potassium levels were measured in the patients every 4–8 weeks as decided by their nephrologists. Hypokalemia was defined as serum potassium level below 3.0 mmol/L. Baseline data including age, gender, comorbidities, underlying renal diagnosis, duration of dialysis, duration and dosage of spironolactone, were recorded. Average blood pressure and serum potassium levels, 6 months before and after spironolactone treatment, were computed. Dialysis adequacy indices, daily ultrafiltration volume, urine output, residual renal function, and the use of medications that might affect potassium balance, including diuretics, potassium supplement and angiotensin-converting enzyme (ACE) inhibitor, were also reviewed. Residual glomerular filtration rate (GFR) was calculated as an average of 24-hour urinary urea and creatinine clearance [14].

Statistical analysis

Statistical analysis was performed using SPSS version 11.0 (SPSS Inc., Chicago, IL, USA) for Windows. Results are expressed as mean ± standard deviation unless otherwise specified. Comparisons between pre- and post-spironolactone data were performed using paired Student's *t* test. Correlations between continuous variables were assessed by Spearman's rank correlation test (r = correlation coefficient). A p value of less than 0.05 was considered statistically significant. All probabilities were two-tailed.

Results

The baseline demographic and clinical characteristics of the 12 patients are summarized in Table 1. Patient demographics were similar to that of the CAPD population of our dialysis unit as published previously [15,16]. The baseline serum potassium level was 3.30 ± 0.26 mmol/L. Five patients required regular oral potassium supplementation; the average dosage was 19 ± 7 mmol per day. Six patients received frusemide; the average dose was 222 ± 69 mg per day. Of the seven patients with preexisting cardiovascular diseases, five were on concomitant ACE inhibitor therapy.

All patients received spironolactone 25 mg daily; the median duration of treatment was 20 weeks (range, 8–26 weeks). After 3 months of spironolactone therapy, there was an insignificant increase in average serum potassium level from 3.30 ± 0.26 to 3.46 ± 0.38 mmol/L (Table 2) (paired Student's *t* test, p = 0.28).

Table 1. Demographic and baseline clinical data of the patients (n = 12)

Sex (M:F)	1:11
Age (yr)	57.8 ± 17.9
Duration of dialysis (mo)	44.6 ± 35.7
Body height (cm)	155.2 ± 7.3
Body weight (kg)	52.9 ± 6.1
Mean blood pressure (mmHg)	101.9 ± 16.5
Renal diagnosis (n)	
Glomerulonephritis	2
Diabetic nephropathy	6
Polycystic kidney	1
Others/unknown	3

Table 2. Residual renal function, dialysis adequacy indices and nutritional parameters at baseline and 6 months after spironolactone treatment

	Baseline	6 months after treatment	p
Daily urine output (L/day)	0.53 ± 0.75	0.27 ± 0.52	0.021
Residual GFR (mL/min/1.73 m^2)	1.59 ± 1.88	0.67 ± 1.02	0.014
Daily exchange volume (L/day)	6.17 ± 0.58	6.33 ± 0.78	0.8
Daily ultrafiltration volume (L/day)	0.99 ± 0.58	0.36 ± 0.61	0.01
Weekly total Kt/V	2.04 ± 0.55	1.97 ± 0.34	0.5
NPNA (g/kg/day)	1.02 ± 0.30	0.94 ± 0.26	0.4
Serum albumin (g/L)	31.7 ± 3.7	31.4 ± 5.6	0.9

GFR = glomerular filtration rate; Kt/V = index of dialysis adequacy; NPNA = normalized protein nitrogen appearance.

Changes in serum potassium of individual patients are depicted in Figure 1. Two patients no longer required oral potassium supplement, while three others were still dependent on regular supplementation with the average dosage at 13 ± 5 mmol per day. After spironolactone treatment, there was no significant change in the mean arterial blood pressure (102 ± 17 *vs.* 102 ± 15 mmHg; $p = 0.97$). Changes in mean arterial blood pressure of individual patients are depicted in Figure 2. The change in serum potassium level was slightly less in patients with diabetes (0.12 ± 0.53 *vs.* 0.20 ± 0.49 mmol/L; $p = 0.5$) or with concomitant loop diuretic therapy (0.13 ± 0.46 *vs.* 0.18 ± 0.56 mmol/L; $p = 0.6$). The increase in serum potassium level was more marked in patients on oral potassium supplement (0.29 ± 0.75 *vs.* 0.06 ± 0.19 mmol/L; $p = 0.6$) or ACE inhibitor treatment (0.27 ± 0.55 *vs.* 0.05 ± 0.44 mmol/L; $p = 0.2$). None of the results reached statistical significance because of the small sample size. Serum potassium level after spironolactone treatment was not related to baseline urine output ($r = –0.212$, $p = 0.5$) or residual GFR ($r = –0.282$, $p = 0.4$).

Spironolactone was well tolerated amongst our CAPD patients and no adverse effect was reported. No episode of hyperkalemia was noted during the period of spironolactone treatment.

Discussion

In this study, we found no significant change in the serum potassium level of CAPD patients after administration of spironolactone. Our results indicate that spironolactone is not effective in the treatment of hypokalemia in CAPD patients. Nevertheless, spironolactone was well tolerated with minimal adverse effects in this group of patients. These results suggest that low-dose spironolactone may be administered with caution to CAPD patients with cardiovascular indications.

The use of aldosterone antagonist in renal patients has become a hot topic recently. Coronary artery disease and congestive heart failure are common in patients with chronic kidney diseases [17] and those on dialysis [18,19]. The renin-angiotensin-aldosterone system plays a key role in the pathophysiology of congestive heart failure [20,21]. Aldosterone does not only promote salt retention, but is also an important mediator of myocardial collagen deposition [22,23]. Spironolactone, a competitive inhibitor of aldosterone, reduces the mortality and morbidity in patients with congestive heart failure [24–26]. The indiscriminate prescription of spironolactone, however, has recently been implicated in causing an increase in hyperkalemia-associated morbidity and mortality, especially in patients with preexisting renal impairment [27]. Therefore, spironolactone is generally contraindicated in patients with advanced renal insufficiency.

Reports are scanty on the use of spironolactone in dialysis patients [28,29]. Our result is similar to that of Saudan et al [28] who found that low-dose spironolactone did not change the mean serum potassium level or was not associated with an increased frequency of hyperkalemia in hemodialysis patients. An accompanying editorial to the study by Saudan et al concluded that spironolactone can be safely

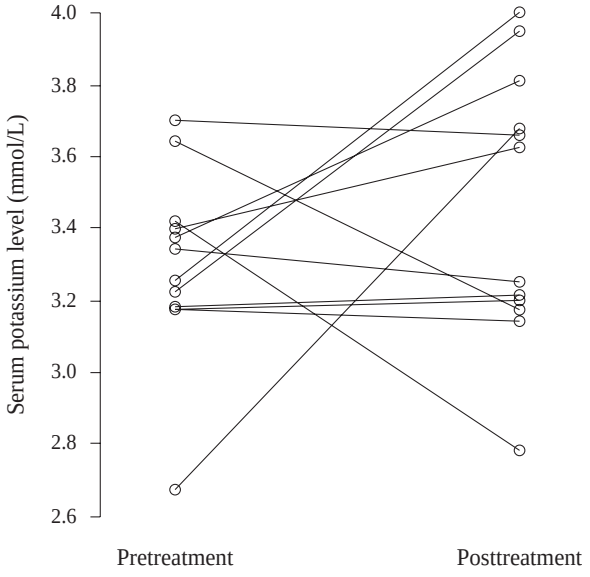

Figure 1. Serum potassium levels before and after spironolactone treatment.

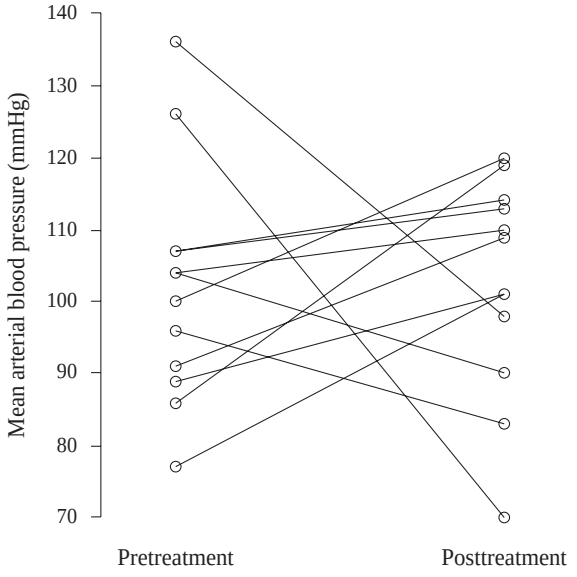

Figure 2. Mean arterial blood pressure before and after spironolactone treatment.

administered to stable hemodialysis patients, and may be considered as a treatment option for chronic hemodialysis patients with heart disease [29]. It is generally agreed that peritoneal dialysis is less effective in removing potassium, and our results suggest that this can probably be extrapolated to CAPD patients.

There are several limitations to our study. Because of the small sample size of our study, we did not have adequate statistical power to detect a small but physiologically significant change in serum potassium level. We did not assess the compliance to spironolactone treatment or potassium supplement. The retrospective nature of this study did not allow us to perform detailed balance study on the potassium intake and the change in urinary, dialysate, and gastrointestinal loss of potassium before and after spironolactone treatment. As none of our patients had chronic diarrhea or vomiting, and the average daily urine output was less than 700 mL, the lack of effect of spironolactone suggested that poor dietary intake was probably the major cause of hypokalemia in our patients. It is important to note that most of the patients in this series had little residual renal function. Therefore, one needs to be cautious when extrapolating our results to patients with substantial residual renal function.

In summary, we found that spironolactone had negligible effect on the serum potassium level of stable CAPD patients. Spironolactone was well tolerated in these patients with minimal residual renal function. The therapeutic role of spironolactone in CAPD patients with congestive heart failure or other cardiovascular diseases may warrant further study.

Acknowledgments

This study was supported in part by the CUHK research account 6901031. The authors declare no conflicts of interest.

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